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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	5

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire Three month(s), ~~or thirty days~~, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1 - 10 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-10 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). (two)
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

☆ U.S. GPO: 1998-404-496/40517

DETAILED ACTION

1. The preliminary amendment and IDS filed 11/15/96 and 3/17/97 have been entered.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-3 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Hershenson et al (B).

Hershenson et al disclose a stable liquid pharmaceutical formulation of recombinant IFN β with a stabilizing polyol (glycerol) and a buffer that maintains pH within a range of about 2-4 (col 5, lines 4-11, and col 19, Tables 1 and 2). The patent teaches that the IFN β formulations can further comprise mannitol and human serum albumin and that mannitol can be present at a concentration of from 0.025 -10 % (i.e. from 2.5 - 100 mg/ml) (col 9, line 21-31). Hershenson et al also teach a method of preparation of the formulation (col 9, lines 35-49).

4. Claims 1-2, 5, 7 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Cymbalista et al (A).

Cymbalista teach a stable liquid IFN β pharmaceutical formulation that has a polyol (mannitol), human serum albumin and a buffer (acetate) that maintains the pH at 3.5 (col 1, lines

47-60, and col 2, lines 36-45). Cymbalista teach a formulation of approximately 0.5 MIU/ml (col 2, line 40-45) which can reasonably be interpreted to mean 0.6 MIU/ml. The patent also teaches a process for the preparation of such a pharmaceutical composition (col 2, lines 18-29).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cymbalista et al (A) in view of Hershenson et al (B) and Rideout et al (C).

The claims are to a liquid pharmaceutical formulation that has IFN β, a polyol, and buffer that maintains the pH between 3-4 (Claim 1), wherein the polyol is mannitol (claim 2), the IFN β is recombinant (claim 3) and at a quantity between 0.6-1.0 MIU/ml (claim 4), the buffer is acetate (claim 5) and at a concentration of 0.01 M, wherein the formulation also comprises human albumin (claim 7), wherein the formulation comprises 1 MIU/ml of interferon beta, 54.6 mg/ml of mannitol, 0.5 mg/ml of albumin in a solution of 0.01 M acetate buffer at pH 3.5 (claim 8). A process for the preparation of the liquid formulation of claim 1 (claim 9), and a hermetically sealed in sterile conditions comprising the liquid formulation according to claim 1 (claim 10).

Cymbalista et al teach a stable liquid IFN β pharmaceutical formulation that has a polyol (mannitol), human serum albumin and a buffer (acetate) that maintains the pH at 3.5 (col 1, lines 47-60, and col 2, lines 36-45). The patent also teaches a process for the preparation of such a pharmaceutical composition (col 2, lines 18-29). Cymbalsita teach that the sterile IFN β formulation is added to sterile glass vials, followed by lyophilization and sealing (col 2, lines 30-33). However, the patent does not teach recombinant interferon at 0.6-1 MIU or a composition that has 54.6 mg/ml of mannitol, 0.5 mg/ml albumin or sealed containers with the liquid formulation.

Hershenson et al also disclose a stable liquid pharmaceutical formulation of IFN β with a stabilizing polyol (glycerol) and a buffer that maintains pH within a range of about 2-4 (col 5, lines 4-11, and col 19, Tables 1 and 2). The patent further teaches that the buffer is at a concentration of 1 to about 50 mM (col 9, lines 13-20). Hershenson et al disclose that the concentration of the recombinant IFN β can be within the range of 3 MIU/ml (low dosage) to 12 MIU/ml (normal dosage) (Col 8, lines 47-60). The patent teaches that the IFN β formulations can further comprise mannitol and human serum albumin and that mannitol can be present at a concentration of from 0.025 -10 % (i.e. from 2.5 - 100 mg/ml) (col 9, line 21-31). Hershenson et al also teach a method of preparation of the formulation (col 9, lines 35-49). However, the patent does not teach a formulation that has acetate buffer, human albumin at 0.5 mg/ml, or a container with the liquid formulation.

Rideout teach that pharmaceutical formulations that contain IFN (col 4, line 12) may be in the form of sterile, aqueous solutions that contain buffers and that these solutions may be sealed in ampules or vials (col 5, line 39-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to modify the liquid IFN β formulation of Cymbalista by using recombinant interferon as taught by Hershenson et al, because recombinant proteins are easier and less expensive to produce. It would have been obvious to modify the Cymbalista formulation by using mannitol at a concentration of 54.6 mg/ml because Hershenson teach that the mannitol can be present in a range from 2.5 -100 mg/ml and 50 mg/ml is about midway between this range. Small changes in the concentration of mannitol would not be expected to influence the activity of IFN β because mannitol is an excipient that is used because it is inert and does not affect the cytokine's activity to any great extent. One of skill in the art would also have found it obvious to modify the Cymbalista formulation of approximately 0.5 MIU/ml (col 2, line 40-45) by using a higher concentration such as 0.6-1 MIU/ml of IFN β becaue Hersshorn et al teach that IFN β can be present at concentrations of 3 MIU/ml or higher in liquid formulations. One of skill would have wanted to increase the concentration of IFN β because more concentrated doses take up less volume and can be stored and transported more economically. It would have been prima facie obvious to one of skill in the art to modify the formulation of Cymbalista by using 0.05% human albumin as because Hershenson et al teach that human albumin may be used as a stabilizer in

IFN β liquid formulations at concentrations from 0.025- 10% (0.25- 100 mg/ml, col 9, line 25-31).

It would also have been prima facie obvious to one of skill in the art to modify the sealed containers of Cymbalsita et al by sealing the container before lyophilization to store the formulation as a liquid in sterile sealed containers because Rideout et al teach that IFN β can be stored in this way and a liquid formulation would be easier to use than one that had to be reconstituted from a lyophilized state.

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mukul Ranjan whose telephone number is (703)-305-4060. The examiner can normally be reached between the hours of 8:00 A.M. to 4:30 P.M. EST Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached on (703) 308-2957. The fax phone number for this Group is (703)-308-0294 .

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)-308-0196.

MR

Mukul Ranjan, Ph.D.
5/7/97

Stephen Walsh

STEPHEN WALSH
SUPERVISORY PATENT EXAMINER
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